Remarks

In summary, claims 1-3, 5-9 and 12-101 are pending in the present application, however claims 2, 12, 20, 25-32 and 34-101 are withdrawn from further consideration as drawn to non-elected species. Claims 1, 3, 5-9, 13-19, 21-24 and 33 have been examined and stand rejected. In a telephone interview held June 20, 2005, Examiner Wessendorf indicated that claims 2, 12, 20, 94 and 95 would be rejoined and that claims 1-3, 5-9, 12-24, 33, 94 and 95 would be allowable if amended to incorporate the feature of variant peptides based on SEQ ID NOS:46-105 of Table III.

Here, claims 1, 3, 5-9, 13-19, 21-24 and 33 are rejected as not fully enabled by the specification. The Office Action asserts that the specification enables methods using a "biased library based from a native G protein Gα-subunit carboxyl terminal and specific peptide library for the candidate compounds," but not all types of native Gα subunit carboxyl terminal. In essence, the Office is rejecting methods to a screening method based on an inability to disclose in advance all compounds which could be screened using the method.

The Office indicates that the rejections are maintained regarding enablement because the Applicants assertedly stated that the examples are based on the "**single** carboxy terminal sequence of Gαt (SEQ.ID.NO.:139)," citing page 21 of the previous response (emphasis in original). First of all, that is not what

Applicants stated. In response to the erroneous statement in the Office Action that libraries were based on "a wide range of biologically active receptors," Applicants explained that the exemplary libraries were not based on the receptor but were based on G protein sequences. To explain how this worked, Applicants used "'the carboxy terminal sequence of Gαt (IKENLKDCGLF;SEQ ID NO:139),' for example" (emphasis added) as an example of how the invention worked. Therefore Applicants stated that SEQ ID NO:139 was an example of what the exemplary libraries were based on, since the Office Action was clearly based on a lack of understanding of the difference between GPCR and G proteins. Applicants submit that it is not proper to limit the claims to a single example based on this statement. Second, the specification clearly contains more than a single example. Applicants urge the Examiner to review the specification with particular attention to the working examples.

Applicants will list and outline some of the examples here to assist the Office in understanding the breadth of the disclosures of the specification, however these exemplary explanations are not be construed as an exhaustive list of all examples contained in the 111-page specification. Therefore, as an example of what is disclosed in the specification, libraries were created based on Gαi, Gαo, Gαs, Gαq, Gα11, Gα12, Gα13, Gα14, Gα15 and Gαz. These libraries were expressed according to the

methods of the invention. See Example 24, for example. The Office is invited to review the disclosure of screening results in Tables IV-V and IX-XVIII, for example, which provide proof that the methods work (libraries can be created, expressed, screened, and results obtained for) at least, for Gαq, Gα11, Gαs, Gαt, Gα12, and Gα13.

The specification describes the actual production of a Gα11-based library for which panning results are provided in Table IV. The specification provides detailed instructions for production of libraries in Example 1, which exemplified a Gαt library. Results of screens using that library on two forms of rhodopsin are provided in Tables IX, X and XV. Working Example 2 shows that additional library constructs were made using these methods for the sequences in Table VII, i.e., Gαs, Gα11, Gα12, Gα13, Gα15, and Gαz based libraries. A Gαq library was produced. Results of three separate screens with that library on three preparations of PAR1 GPCR are provided in Tables XI, XII and XIII. The Gαs library was screened against B2 adrenergic receptor with the results presented in Table XIV. In Example 11, PAR1 GPCR was screened against the Gαt, Gα12 and Gα13 libraries with results presented in Table XVI. The PAR1 receptor also was screened with Gα11 (Table XVII). The Gαt library was rescreened in a competitive assay and the peptides in Table XVIII were identified. These are all working examples where libraries were

constructed. The Office is invited to review the data obtained when the indicated libraries were expressed and screened. To doubt that libraries based on G protein sequences can be produced, expressed, and screened according to the methods claimed is simply not supportable.

The Office has referred to the claims as encompassing using "any or all" types of native Gα peptides. The G protein sequence is selected based on the GPCR which is selected. In that respect, any Gα peptide that binds to the GPCR could be used to design a library. Once the GPCR is chosen, a library would be formed based on Gα peptides that bind the chosen GPCR. If a different GPCR were chosen, a different Gα protein might be used to design the library. Thus, although any Gα peptide could be used in the screen, the claims still are limited to Gα peptides that bind to the GPCR. A pair of GPCR/Gα peptide is selected because they are known to bind. If they are known to bind, it is reasonable to expect that a library based on this Gα peptide (which binds to the GPCR) would yield results as described.

The Office refers to the "broad scope" of the components and method steps but does not state what this scope is asserted to be. Applicants submit that the scope is broad only in the senses that the screen can work with any GPCR/Gα pair that binds, but not broad in that any GPCR should be screened with any Gα peptide whether it binds that GPCR or not.

Next, the Office refers to Gαt as including "a huge species from one type of Gα." Applicants do not understand the significance of this statement. Gαt is a species of Gα (see specification, paragraph 13, lines 13-15, which refer to 16 unique Gα subunits known at the time this application was filed). How Gαt can be a "huge species" is not explained, therefore Applicants are not able to respond to these statements.

The Office asks Applicants "[h]ow much more for the numerous different types of species (e.g. Gαt) included in G-alpha subunit carboxyl G-protein?" Applicants do not understand this question. Although Gαt is provided as an example of a species of Gα different from Gαt, Applicants assume the Office is referring to a perceived large number of Gα subunit species. The specification lists 16 known Gα subunits and provides working examples for libraries made based on the carboxy-terminal sequence of a number of them. Applicants created libraries based on most of the 16 known Gα subunit carboxyl termini. The Office cannot provide any reason why the same method would not work for the remaining subunits, which are not "numerous."

The Office then indicates that a "listing of every possible Gαt, a species of Gα, from a single native G protein" does not enable every species in a genus." First, a single native G protein has only one Gα. Sometimes this Gα is Gαt. Therefore, there is no way to list more than one Gαt from a single native

G protein. Second, what species and what genus this hypothetical listing would not enable is not explained.

Applicants will describe how these types of screens function with this one example in the first instance, then point to numerous other examples in the specification as filed, and then explain why, since all the GPCR/Gα pairs function in exactly the same way, these examples are more than sufficient to enable the screen as claimed. The examples provided here should not be interpreted by the Office as limiting with respect to the disclosures of the specification.

As discussed in Example 7 of the specification, a Gαt-based library was screened against rhodopsin receptors. Gαt was selected because it is known to bind the rhodopsin receptor. Light-activated and dark-adapted receptors were panned with the Gαt-based library and the sequences in Tables IX and X were found to bind with high affinity. In the two-step screen, these high affinity-binding peptides are used in a competitive screen of other compounds to discover molecules that bind with high affinity-affinity at least as great as that of the peptides found in the first screen. This is illustrated in Example 14 with rhodopsin and peptide 8 using a Gαt library.

The specification is not limited to rhodopsin/Gαt screens only, as the Office asserts. Thus, the comments concerning every possible Gαt or other species of Gα which are not enabled does

not relate to the specification here. A careful reading of the application as filed shows that the following examples of GPCR/Gα pairs have been provided in the detailed description and examples:

1. Light activated rhodopsin/Gαt; ¶¶96-101; Examples 7, 10, 14, 18, 34
2. Dark-adapted rhodopsin/Gαt; ¶¶96-101; Examples 7, 10, 14, 18, 34
3. Human thrombin receptor (PAR1)/Gαt; ¶¶102;
4. B_2-adrenergic receptor/Gαs; ¶113, Example 9
5. Adenosine A1 receptor/Gαi; ¶113,
6. $GABA_B$ receptor/Gαi; ¶113,
7. Muscarinic M2 receptor/Gαi; ¶113
8. PAR1/Gαi; ¶155
9. PAR1/Gαq; ¶155; Example 8, Example 22
10. PAR1/Gα12; ¶157
11. PAR1/Gα11; Example 20
12. PAR1/Gα13; Figure 19.

Examples were provided showing screening of rhodopsin/Gαt, as the Office states. However, PAR1 from three different sources was screened with a Gαq-based library (see Example 8), PAR1 was screened against Gαt-, Gα12- and Gα13-based libraries in one-step and two-step assays (see Example 11) and against a Gα11-based library (see Example 20). Several of the peptides which were discovered by these screens were tested for activity (Examples 25-31) and were found to be active. Small molecules were

screened (Example 36) and the molecules discovered by the screen tested for activity and specificity (see Examples 37-38).

Furthermore, Gα peptide-based libraries were constructed and expressed, showing that these expression systems do work. Example 24, which describes how this was done for the Gα peptides Gαi, Gαo, Gαs, Gαq, Gα11, Gα12, Gα13, Gα14, Gα15 and Gαz, as well as a control library based on GαiR. For the Office to assert that the disclosure of this application is limited only to Gαt simply is not supported. The specification lists, describes and provides detailed examples and results for several GPCR/Gα peptide pairs, and lists many examples of appropriate Gα peptides upon which to base libraries in Tables II, III and VI, for example.

Applicants therefore submit that any skilled person who reads this specification would be able to choose <u>any</u> GPCR and <u>any G protein that binds to</u> that GPCR, and produce a peptide library based on the Gα subunit of that G protein to screen for binding to that GPCR. Not only does the specification describe many of the known GPCR/G protein pairs and provide detailed examples and methods for numerous different GPCR/Gα peptide pairs, with results given, but the specification describes why the members of this highly similar and related class of receptors and their highly related binding partners, the G proteins, all behave in an analogous fashion. When the binding pairs all behave the same way as far as the screening method is concerned, even one example is sufficient to enable the whole class of related binding pairs. But the specification here has not provided only one example but at least seven detailed working examples plus lengthy discussion concerning methods applicable to the entire class of GPCR and G proteins, guidance in the form of lists of available and known binding pairs, and comprehensive tables listing dozens of Gα peptide carboxy-termini on which to base libraries.

A comprehensive list of known Gα subunits with sequences of their carboxy termini provided (Tables II and III) specifically discloses a large number of species in the genus of Gα subunits known at the time. The sequences of these Gα subunits are known; the carboxy-terminal sequences are provided. This voluminous disclosure provides more than sufficient guidance for a person skilled in the art to find a Gα subunit that binds to the GPCR of interest, or choose from among the known Gα subunit binders, and to construct a peptide library of variants based on the carboxy terminal sequence of that Gα type.

The Office Action states that the disclosure of Gαt would not lead the skilled person to any particular species of a Gα carboxyl peptide of a G protein. Applicants disagree with this blanket statement, but believe that the Office's concern regarding enablement is with respect to all species of Gα that are not Gαt. The Office apparently believes that the disclosures of the specification are limited to Gαt and therefore only Gαt screens are enabled. This specification discloses a GPCR screen that uses a library based on the Gα carboxy terminus sequence of a G protein that binds to that GPCR, provides lists of GPCR, lists of G proteins and pairs of GPCR/G proteins that bind each other, along with seven working examples of different binding GPCR/G protein pairs (and many others described) combined with explanations of why all the GPCR/G protein combinations that bind are analogous and work the same way by binding on the intracellular face of the GPCR.

The disclosure goes far beyond merely disclosing Gαt. It describes the entire genus of Gα subunits, both generally and with numerous examples, and how to use them to create libraries for screening the appropriate binding GPCR. GPCR are well-known proteins. What is more, the relationship of GPCR to G proteins is known--one of skill knows which GPCR bind to which G protein.

One need only refer to a college textbook of the period such as Lewin, B., Genes VII Oxford University Press 2000, chapter 26, in particular pages 809-811 to recognize that this type of information was available to college students. Figure 26.10 provides a chart of G proteins and examples of receptors with which they interact. The person of skill in this art, would have been a Ph.D. with substantial post-doctoral training who would have been familiar with the GPCR/G protein pairs that are known to interact with each other. Although the specification lists several different examples of Gα subtypes and dozens of specific examples, this class of proteins is so well known and so well-studied over the past two decades that it is ludicrous for the Office to require a complete listing for the skilled person to recognize what GPCR or G proteins are. And if a worker does not know if a particular GPCR binds to a particular Gα subunit, it is a routine and simple matter to test binding. As described in the specification, binding assays such as radioligand assays, see ¶167, are routinely used. The binding site on the peptide can be determined using photochemical cross-linking, peptide residue substitution, receptor-peptide cross-linking, study of cleared peptide fragments, mass spectrometry or any other known method. See paragraph 168. Nevertheless, the claims here are limited to carboxy-terminal peptides of Gα G protein subunits. Certainly, the voluminous and comprehensive disclosure of suitable Gα carboxy terminal peptides disclosed here are more than sufficient to enable the skilled person to screen any GPCR that binds to at least one G protein Gα subunit, choose a Gα subunit that binds the GPCR and make a peptide library from its carboxy-terminal sequence.

The Office Action mentions that the disclosures do "not take into consideration the numerous variations encompassed by the variant peptides based on said carboxyl subunit of G-protein."

Applicants assume that the Office is not objecting to the fact that the peptide library contains numerous different variant peptides since that is what peptide libraries contain by definition. If the Office is concerned that libraries may be based on variants of G protein sequence, the claims make clear that the library of variant peptides is based on the primary sequence of a native G protein Gα subunit carboxyl terminal peptide sequence "and not based on variants." Persons of skill would have been aware which G proteins (Gα subunits) bound to a GPCR and which sequences on the Gα subunit were implicated in binding. Applicants refer the Office to the specification, paragraphs 4-5, and the references cited therein, which are of record in this case. Carboxy terminal peptides that bind to the GPCR were known in the art and do not need to be specifically listed to enable the methods. The carboxy-terminal 11 amino acids of the Gα subunits were known to be important to GPCR interaction.

The Office refers to "numerous variants." If the Office is attempting to express concern that Gα carboxyl terminal peptides of different lengths may form these "numerous variants" and that these different length peptides would not be enabled, Applicants would like to point out that the claims relate to libraries based on the primary sequence of a native G protein Gα subunit carboxyl terminal peptide and thus are confined structurally to peptides that contain the carboxy terminal amino acid of the subunit and other amino acids of the sequence progressing toward the amino terminus. This is a finite set of peptides from one amino acid to the complete native sequence of a Gα subunit, and not an infinite number of variables with unknown sequence. The claims also are limited functionally to libraries based on Gα carboxyl terminal peptides that bind to the GPCR that is being screened, on a G protein interaction site of that GPCR. Entire Gα subunits

bind to GPCR, as is well known in the art. Therefore, there is no reason to believe that protein folding, for example, might interface with binding in longer peptides because (1) the sequences are limited to native sequences that already are known to bind and (2) the longest possible sequence of the claim, an entire Gα subunit, does bind. Thus, long sequences within the parameters of the claims are enabled. Extremely short sequences such as one or two amino acids may not bind, but if they do not bind they are not encompassed by these claims.

It would not involve undue experimentation for a person of skill, possessing knowledge of G protein/GPCR binding and peptide binding generally to determine how short a peptide could be to fit within these claims, especially since the sequences of the peptides are already known and finite. It therefore would not be a matter of testing all peptides of all lengths and all sequences, but only of testing, for example, the small number of peptides that are carboxy terminal Gα subunit peptides of known sequence for any Gα species. The specification already provides guidance that preferred peptides are about 7 to about 55 amino acids long (specification, paragraph 54), but the Office has provided no reasons for believing that shorter or longer sequences would not be enabled, especially since the sequence length is limited by the claims to the entire length of the Gα subunit, which is known to bind, and to functional (binding) peptides. The specification explains the 3-5 carboxy terminal peptide can be responsible for the specific binding of a Gα peptide (specification, paragraph 13), so there is no reason to believe that libraries based on any binding, carboxy terminal peptide would not work in the claimed method.

If, on the other hand the Office means to express concern that the libraries themselves comprise "numerous variations," then this evidences a major misunderstanding of how high-volume

screens work in modern drug discovery. The libraries screened by workers in this field always comprise a large number of variants, in this case structural variants. The majority of the compounds in the library may not bind, but the purpose of creating a library is not to assemble a collection of compounds that bind--it is to assemble a very large collection of compounds, some of which have a good chance of binding, so that the screen can operate to discover these rare binding compounds. Thus, it is the purpose of the screen to discover within the library a collection of compounds that bind. If the library already contained a small number of known compounds that bound, there would be no point to screening the library at all.

The screen here involves matched pairs of G proteins and GPCR, thus any G protein can be used in the screen, with a GPCR to which it binds. This is clear from the claims, which are limited to methods where a Gα carboxy terminal peptide that binds the GPCR is used to produce a library of peptides based on the sequence of that Gα carboxy terminal peptide. Thus, in practical terms the claim does not encompass any GPCR with any Gα, but only any pair of GPCR with a Gα that binds it. So, because the library is based on a structure (sequence) that binds, there is an increased chance that the library will contain a binding sequence.

The Office seems to be concerned that one library would not predict results in an assay using any library, especially those having no defined structure. The application has not defined only a single library, but dozens of them, and provided complete working examples of at least seven libraries. The claims do not relate to a library having no defined structure. The library is based on the primary sequence of a carboxy terminal peptide from a Gα subunit that binds to the GPCR being screened against. A large number of exemplary Gα subunit carboxyl termini peptides

have been disclosed-Applicants submit that this large disclosure is more than adequate to enable the claims.

The Office remarks that in the "single, defined compound, library, a single residue variation did not produce the desired object of the invention." Page 7, lines 18-19. Applicants do not understand this criticism. Since the Office refers to a "residue," Applicants assume the library is a peptide library. Applicants provided working examples of several peptide libraries, described how they were made and used, explained how to make and use analogous libraries from other peptides, and listed dozens of exemplary peptides. Applicants did not disclose only a "single, defined" library.

Assuming that one peptide in the library that varied from the native sequence in one residue only did not bind the GPCR with high affinity, this would not be relevant to whether the screen works. When screening a library, it is assumed that most compounds in the library will not bind strongly. When 10^9 peptides are screened and a few dozen are discovered to be strong binders, then nearly 10^9 peptides have produced a negative result. This was the case with the rhodopsin/Gαt screen which the Office states <u>is</u> enabled. Examples provided show that the method works with at least several GPCR/Gα pairs to identify strong binders.

The Office Action states that the assay method is one of the unpredictable factors in the "broad scope of the method." The entire method of the claim is an assay method. What method steps are asserted to be "unpredictable" is not stated in the Office Action. Therefore Applicants cannot respond to this criticism and request an explanation of its meaning.

The Office remarks that the "variations in the library and library of candidate compounds" are determinative of the unpredictable effects of the method. This comment also is

confusing. A library is a collection of compounds. Therefore, the compounds in a library are varied. This is inescapable and this allows the method to work--it in not an indication of unpredictability. Further, the peptide libraries of the claim are not just any collections of any peptides. The claims require that each peptide library be based on a sequence of a Gα subunit that binds to the GPCR. The Gα subunits that bind to a GPCR are either known or readily discernable and form a finite and rather small class. What makes the office doubt that a library of peptides based on the primary sequence (structure) of a known binder is too unpredictable to work when the applications showed that it did work seven times with seven different GPCR/Gα pairs is not stated in the Office Action. The only reasons given for this alleged unpredictability are that the library is undefined, which is not true and that only one Gα was exemplified, which also is not true.

The Office repeatedly insists that the "known, single and defined library" cannot predict the undefined structureless library which is asserted to be claimed. Applicants have explained that the library, is based on the carboxy terminal primary sequence of a known Gα subunit that binds to the GPCR being screened against. The claimed libraries are defined by structure. First, one selects a GPCR, then one selects a G protein that binds to the selected GPCR (not any G protein), then one provides a library based on the primary sequence of the Gα carboxy terminus of that G protein (not any G protein) that binds to the GPCR (not any sequence, but one that binds). The G proteins that bind to a given GPCR are known or readily discernable, and in any case would be selected from a small, finite and known group. The sequences are known or readily discernable. At least seven complete, working examples with different GPCR/G protein pairs are given, along with voluminous

guidance, both generally and for specific sequences, which allows the same methods to be used with the entire class, which all work the same way.

The Office states that in an HIV assay, the virus being assayed is known. Here the binding being assayed in the claims also is known--that binding is binding of a GPCR-Gα subunit pair known to bind and binding of that GPCR to Gα subunit analogs in a library designed to be structurally similar to the binding Gα. The Office states that a specific assay method is adapted for determination of the HIV virus irrespective of "the type of blood samples." This assay is adapted for determination of GPCR/ G protein binding at the intracellular face, irrespective of the type of sample being screened. If a peptide does not bind, or if it does bind to the GPCR, the assay is able to detect this. The Office states that an HIV assay does not screen for any type of virus. Here the assay does not screen for any type of binding but only for binding to a chosen GPCR at the G protein-binding location. The analogy was aimed at explaining to the Office that the screening methods workability does not depend on whether a particular sample being tested is positive or negative, just as for an HIV assay. The Office has not understood that the assay here is testing a known binding phenomenon, just as would any assay for detecting HIV antibodies, for example. Both assays test a known, specific phenomenon and determine whether it is present in unknown samples, regardless of the "type" of sample.

The Office states that the invention is a screen for a particular event but the scope of the claims is "huge" because screening can only be achieved in a library "of known constituent." Applicants respectfully submit that the library is defined in the claim as a library based on the primary sequence of a native G protein Gα subunit carboxyl terminal peptide sequence that binds to the GPCR being screened, on the G protein

interaction site of the GPCR. The library is not based on any sequence or on a variant of G protein sequences, but on the native sequence of a Gα subunit that binds. Pairs of GPCR/ G protein that bind are known, as discussed above, or can be easily determined, and it has been taught here that sequences of different lengths bind to the GPCR, including entire Gα subunits.

The Office concedes that Table III presents specific examples of different G protein sequences that can be used for library construction but criticizes the claims as not reciting only G proteins but a variant library based on the different G proteins. The reason for this criticism appears to involve the fact that the claims do not recite the compounds from Table III. Thus, it is not clear why the claims are rejected.

If the Office means to imply that only sequences that are specifically disclosed in Table III are enabled as library members, the Office has drastically misunderstood the invention and the claims. The claims require that the Gα subunit carboxyl terminal peptide-based library be based on a peptide (i.e. a Gα subunit) that binds the GPCR being screened against. Not all the Gα peptide examples in Table III bind to each GPCR. Thus, requiring that such be recited in the claims as the peptides of the library would result in a largely non-operative and pointless screen. For any selected and known GPCR, it likely would already be known whether the sequences of Table III bound or not. There would be no reason to screen Gα subunit peptides if the Gα subunit they were part of did not bind. If the Gα subunit did bind, it would be pointless to screen just that one peptide. The point of assays generally is to test unknown compounds so that new information may be obtained. Screening has no point when the result is known beforehand.

If the Office means to imply that only libraries that are based on the sequences disclosed in Table III are enabled, this

again evidences a misunderstanding of how the assay is designed to work and the state of knowledge in the art. The assay screens a GPCR against a collection of compounds (a library). This collection of compounds are structurally-based (sequence-based) on a peptide from the carboxy terminal of a G protein. Not any G protein, but a G protein that binds the GPCR. The peptide is a Gα carboxy terminal sequence. (Discussion of different length peptides is found above.) This Gα sequence is a known or discovered binder of the GPCR. All GPCR bind G proteins, and bind at the same place to Gα carboxyl terminal sequences (and also to other locations of the G protein). Since all GPCR bind in the same way to certain known sequences, any GPCR can be screened if one uses a library that is based on one or more of these sequences. Since G proteins and their sequences are well-known in the art, it would not require undue experimentation for a skilled person to choose any Gα carboxyl terminal sequence that binds and to base the library on this sequence. The Office has stated no credible reason why the methods which work with the numerous exemplified peptides would not also work with any peptide of the same class with the functional and structural limitations in the claims.

The Office states that the disclosure of examples of Gα peptide is not sufficient to enable the claims because the claims also recite "a variant library based on" the G proteins and not merely the G proteins themselves. Page 9, lines 10-11. The Office admits that the specification discloses many examples of peptides upon which libraries are constructed (see ¶¶ 114, 118 which use this terminology and Examples 1-2) but will not allow that such libraries are enabled. The specification describes the "variant library" or "library of variant peptides" and how to construct such libraries based on the native sequence. It appears that the Office is requiring applicants to specifically

disclose each and every library to be claimed, simply because the members of the library are "variants" based on a native sequence.

It may be useful here to explain what a library of variant peptides is, as understood by one of skill. The term "variant" in the specification does not mean that the claimed library could be based on a variety of unknown "variant" peptides--the claims specifically recite that the library of peptides is based on a native G protein sequence that binds to a GPCR. It means that the library is composed of variants based on the stated peptide sequence. As such, the library contains "variants" of the peptide on which it is based. Thus, a library of variant peptides is a library of structural variants and is described as such in the specification; it is not a collection of various libraries of undetermined nature, but a defined library containing variants based on the primary sequence of a known GPCR binder. Applicants urge the Office to reconsider these claims.

The Office next states that construction of peptide libraries is known "only if the compounds present in the library is known such that a library (not variants) can be made." Page 10, lines 7-8. This criticism shows a major understanding of the art of library screening in general and the invention in particular. A library <u>is</u> a group of <u>variants</u>. The quoted statement implies that the only enabled library is one where the compounds in the library are known. First, the Office has admitted that the Gαt-based library is enabled, but this admittedly enabled library also is a library of variant peptides based on SEQ ID NO:139. It contains <u>variants</u> of the sequence of SEQ ID NO:139 which were not individually sequenced and disclosed prior to screening. It does not contain only the disclosed sequence of SEQ ID NO:139, but many millions of <u>variants</u> on that sequence. How to make this library of variants based on a known

sequence is described in detail in the specification and forms part of the art generally.

Second, to reject this application because the library contains peptide variants does not make sense. The examiner is urged to review the definition of a peptide library which is as a collection of cloned peptides, frequently consisting of all possible combinations of amino acids making up an n-amino acid peptide. Thus, peptide libraries are collections of variant sequences by definition. The fact that the library is composed of many variants does not mean that it cannot be made. If the prototypical peptide library of the above definition, which contains all possible combinations of amino acids, can be made, the library of variants of a known GPCR-binding sequence also can be made, especially given the guidance in Example 1 and its cited art.

The Office Action seems to base arguments either that libraries do not or cannot contain peptide variants or that only libraries which contain only defined compounds can be enabled, or both. To require that Applicants specifically name all compounds present in a library that may contain 10^9 different peptides or more is unrealistic. When using a library for screening, once a binder is found, the particular sequence responsible for the binding is determined and identified by sequence. It would be a lifetimes' work to individually clone and sequence all a million library members. The advantage of screening a library rather than individual compounds is that many millions of compounds may be screened rapidly, without having to identify each compound first, and test them individually.

The Office requires sufficient information to be disclosed in the specification such that a library, but not variants, can be made. As discussed above, a library is a collection of variants of a molecular structure. One cannot make a library

without making variants. In this case the library is a collection of peptides that are variants of the native Gα sequence on which it is based. The library is made as described in the specification and exemplified in Examples 1 and 2. Paragraph 114 of the specification describes a preferred library which contains peptides with some residues identical to the native sequence and others randomly changed, to create a collection of peptides which contain similarities to the native sequence. These can only be described as "variants" of the native peptide. Given the detail on how such "variant" peptide libraries are created, the Office's criticism of the library having no definite structure is not correct. The library is based on a specific Gα peptide sequence.

The Office criticizes the state of the art at the time this application was filed as not supporting compounds contained in a library "including variations thereof." Page 10, line 12. Applicants have not claimed any variant of a library. The claims are limited to peptide libraries based on a sequence from a carboxy terminal Gα subunit that binds to the GPCR being screened. Supposed "variations" of these libraries are not recited. The claims recite a library of variant peptides, not a "variant library." A library, as the term is used in this art, is commonly recognized to be a collection of variants. A peptide library is a collection of variant peptides. Since the method of making such a collection of variants has been provided and exemplified by Applicants and also is known generally in the art, the Office is not correct in rejecting this aspect as not enabled simply because the library contains variant peptides.

On page 11, line 15, the Office again refers to the "huge scope of the claimed genus" without defining what this scope is or what genus is referred to, but refers only to unnamed "generic components" which do not define structures such as the variant

peptide library. Applicants assume that this discussion indicates that the Office is objecting to recitation of a (variant) peptide library without reciting a single kind of variant library, the implication being that only a single (unnamed) kind of variant library would be considered enabled. Applicants have amended the claims, for clarity and readability with respect to the library element and consider that the claims are fully enabled in this aspect. The claims do not recite a variant library, but a library of variant peptides. If the Office believes that deletion of the term "variant" from the claim would obviate this rejection, Applicants request to be so informed.

The Office Action states that the "variant peptide library" encompasses substitutions, deletions and combinations thereof. The implication of the statement is that the Office objects to the recitation of "library of variant peptides" without additional limitation describing what substitutions, deletions and combinations thereof in the claim. The assay of the claim involves screening peptide libraries that are based on the sequence of a known binder, structurally. So long as a library is chosen or created that is based on the primary structure of a known binder, it does not matter what the precise variants are. Any structural variant of the known binder, be it a substitution, addition, deletion or any other variant, is a candidate which may be screened.

The Office has pointed to no reason why a library of variants containing substitutions would not be screenable, or a library of variants containing deletions would not be screenable. The Office has said nothing which reasonably casts doubt that libraries of substitutions, deletions etc. could not be screened with this method or would be any less likely to provide a group of potential biding candidates inferior in any way to the

libraries specifically disclosed here. In point of fact, the libraries tested here did include substitutions and deletions, and were shown to work. See, for example, Tables IV and V, which shows examples of screening results for a Gαq library and a Gα11 library, both of which list binding peptides discovered by the screen that are substitutions and/or deletions of the native sequence. Thus, the Office's concern that libraries containing substitutions or deletions or combinations thereof would not be able to be performed by a person of skill given this guidance is misplaced. The Office has provided no credible reason why <u>any</u> library based on the structure of a GPCR binder could not be screened using this method or why <u>any</u> such library would be considered by a skilled person to be either unusable without undue experimentation or unlikely to contain even one suitable candidate for screening. Any structural variant of a known binder is a suitable candidate for testing in this context.

The Office objects to the expression systems as enabled only when the compounds "transforming the system is known or of defined structure." Applicants submit that they have enabled creation of peptide libraries based on native G protein sequences and that once a skilled person has created such a library it is a matter of routine to express it. First of all, the peptides are synthesized as oligonucleotides. A sample construct is given at Table I with a sample peptide. Any peptide's nucleotide sequence can be substituted easily by the person of skill. Table II provides additional oligonucleotide examples. Display expression systems are described at ¶¶ 116-120 and have been shown to work with the methods of the invention to express the peptides. The Office again seems to be requiring that Applicants specifically recite the sequence of all peptides that could appear in a library in order to enable their expression. This is not only unreasonable, but contrary to law. The person of skill can make

peptide libraries containing many millions of different peptides and express them as known in the art or as described in the specification.

Persons of skill had been making and expressing libraries for years as of the time this application was filed. Those persons are able to generate a library of constructs that encode the peptides, for example using PCR, and express them in a system specifically adapted to express a peptide library. The peptides are related to a known or defined structure, but they are numerous and hence not individually recited by anyone creating and expressing such a library. For the Office to assume that methods shown in the specification and in the art incorporated by reference or that a library expression system shown to work many items with many billions of different peptides of random sequence now is not enabled for any other peptides unless the sequences of the entire library are provided individually does not make sense. Many workers have been able to follow the teachings of the art to work with library systems when the art has not taught specifically the sequences of all members of the library.

Expression of one peptide library is equivalent to expression of any other peptide library since they all express large numbers of different peptides, the individual sequence of which is not important until a positive result in the screen is found. Persons of skill know this and know how to express these libraries even for completely random libraries. To argue that only a library of specific, defined, known compounds can be expressed does not make sense when the purpose of a library is to serve as a collection of many millions of different compounds to be screened, and no artisan working with a library is concerned about defining the structure of each member in order to express the library. The Gαt (SEQ ID NO:139)-based library was only one

example of such a library, and is considered enabled although each sequence is not specifically recited.

The Office obviously is equating expression of a peptide library with overexpression in culture of a single protein. This is not appropriate. These library expression systems are designed to express a large number of peptides, even those with random sequences.

The Office refers to a "cited reference," Zwick. Page 13, line 17. This reference was not cited by Applicants and is not of record in this application. No citation for the reference was provided with the Office Action. Applicants assume that the article intended to be cited is Zwick et al., "Phage-displayed peptide libraries," Curr. Opin. Biotechnol. 9:427-436, 1998, which is of record in a related case and is now made of record here in the accompanying Information Disclosure Statement. The Office Action quotes a statement in Zwick which it interprets as evidence of the "highly unpredictable peptide art," presumably with respect to construction and expression of peptide libraries. Zwick et al. did not question the ability of skilled workers to produce or use these libraries. The quoted statement makes clear that these authors assumed the libraries could be used and only stated that the "value" of libraries could be determined by side-by-side comparisons as to which type of library would produce ligands. In order to do these comparisons suggested by Zwick et al., one must be able to screen them. The only "uncertainty" or "unpredictability" that could possibly be discerned from Zwick et al. is what compounds might yield positive results. The "value" referred to is value with respect to which libraries contain the most valuable "ligands," i.e. which libraries would turn out to contain compounds that have similar structure. Any skilled person reading Zwick et al. would recognize that the libraries could be produced, expressed, screened and tested. Furthermore,

the present claims clearly indicate the type of library to be used for the method-ones that are based on the known sequence of a known binding peptide which therefore have a similar or related structure to the known binder.

The Office states that the prior art, for example "Zwick," shows that a phage display library can only be routine if the structure or formula of "a compound" is known. Page 14, lines 18-20. First of all, a library is not "a compound" but many, many compounds. Libraries are routinely used every day in laboratories across the globe, even though the exact sequence of each member is not known by the technician expressing them or screening them. Second, the "structure" of the library is based on the known structure of a known binder (a known compound, if you will) to the GPCR being screened. This has no bearing on one's ability to express the library as described by Zwick et al.

The Office refers to "a compound, as the instant variant library of no defined structure." Page 14, lines 20-21. The Office seems to be indicating that a library is a single compound. A library is a collection of many compounds. Thus, the term "defined structure" does not have the same meaning as it would for a single compound. The defined structure is peptide. Further, the library of the present claims is a peptide library based on the structure of a known peptide binder to the GPCR being screened. That is more than sufficient for the skilled worker to produce a library, express it and perform all the steps of the method which is claimed. Zwick does not indicate that a phage display library can only be routine if the structure or formula of each displayed peptide is given individually.

The Office states that "[i]ncorporating the sequences listed at Table III of the specification to form a variant peptide library would obviate this rejection." Page 15, lines 9-11. Applicants do not understand what this language is intended to

mean, however, in view of the statements made in the telephone interview of June 20, 2005, in which the examiner indicated that libraries based on these sequences were enabled, Applicants are assuming that the sequences do not need to be incorporated to form the library as stated.

In nature, G proteins interact with one or more GPCR on its intracellular portion, via their Gα subunit (and other portions). In order to discover new compounds that have similar or improved interactions with GPCR on this intracellular G protein-binding area, the invention takes advantage of the known structure of G proteins that bind to GPCR and creates a library of compounds based on this structure to test for binding. Therefore, if by this language the Office intended to request that the sequences of Table III do not form the library but rather are sequences on which one can base a library, Applicants still traverse this requirement, for reasons discussed above. To advance prosecution, however, Applicants have added new claim 102, which recites this limitation and request that the Office consider this new claim and reconsider the other remaining claims.

The test for enablement is whether a skilled person could have made and used the invention without undue experimentation. A skilled person could have performed all the steps of this claimed invention in the full scope of the claim with no experimentation, much less undue experimentation. The Office's reasoning is based on the following:

1. Only one library is disclosed. This is not true. Applicants request that the Office review the disclosure of the several libraries and the results from their screens according to the invention.

2. Libraries based on a Gα-coupled receptor carboxy terminus are enabled. There is no such receptor and no such libraries are disclosed or even mentioned. If the Office

intended to refer to libraries based on Gα subunit carboxy terminal peptide sequences, Applicants submit that this is what is claimed.

3. Any or all types of native Gα peptides are claimed. Any native Gα peptide may be used, but the claims are limited to those peptides that bind the GPCR to be screened against for producing the peptide library.

4. Gα subunits are numerous. This may be true, but is not relevant since they are a finite class which is known in the art and has been described and profusely exemplified. Further, the claims are limited to peptide libraries based on the structure of a known binding G protein peptide and each Gα subunit is selective for GPCR it will interact with and each GPCR interacts with one or only a few Gα subunits.

5. The examples are based only on SEQ ID NO:139. This is not true. Applicants request that the Office review the specification.

6. One example does not enable the entire class of GPCR/G protein pairs. Since all GPCR/G protein binding pairs work in an analogous fashion, one example would be enough, however applicants have provided many examples of GPCR/G protein binding pairs.

7. The disclosure of Gαt alone would not lead the skilled person to a particular Gα peptide. The binding pairs of GPCR/G protein are known or readily discernable and many Gα subunits in addition to Gα were disclosed.

8. The libraries are not enabled because they contain variant peptides that are not specifically disclosed. All peptide libraries contain variant peptides that are not individually disclosed. That is their nature and is not relevant to their usability.

9. One variant peptide produced a negative result in the screen, thus introducing unpredictability. The very nature of library screening produces a majority of negative results. The goal is to discern which, if any, of the 10^9 peptides do bind.

10. Variations in the library indicate it is unpredictable. A library is a collection of 10^9 peptides. To speak of the library members as having variations is not meaningful. If all library members were the same (not varied) there would be nothing to screen.

11. In screening assays, the thing being assayed must be known. This invention assays a library based on a known structure for known binding characteristics to a known GPCR.

12. The claims recite "a variant library." The claims do not recite a variant library. Furthermore, the term "variant" does not introduce unknown libraries but only refers to the members of the library as peptides with variant structures based on a known peptide. The construction of such libraries is described and exemplified several times in the specification and is known in the art.

13. The only peptide libraries that can be constructed are libraries in which each member is specifically known. This is patently false. The specification describes construction and use of libraries with millions of members, all of which are variants of a known peptide. Although the library contains many members, there is no point in specifically identifying any particular member or all members to use the library. No skilled person knows the exact identity of every peptide in his library.

14. Only compounds of known structure can be expressed. Peptide libraries containing many millions of peptides constructed as nucleotides are expressed routinely and are exemplified here. Their individual structures are not individually known. If the peptides in a library based on a

known sequence can be expressed, then libraries based on any other sequence to be determined by the experimentor also can be expressed. This type of expression should not be equated with expression of a single protein by a cell system. The systems described and exemplified here are designed to express libraries, not individual proteins.

15. References cited by applicant in a related application to show use of peptide libraries are evidence of unpredictability. This statement was based on a quote stating that the library would have to be screened before results as to the value of the discovered compounds could be known. The reference referred to the content of (structural basis for) the libraries, not any doubts as to their construction or expression. In this invention the library has a structural and a functional basis.

16. A library cannot be constructed, expressed or screened unless the compound on which it is based is known. This is simply not true. Random libraries with no known relation to the binding region are routinely used. However, the libraries of the present claims are based on the structure of Gα subunits and therefore are known. Since G proteins are well-studied and each G protein binds to GPCR in the same general manner as all other G proteins, Applicants submit that any G protein could be used in the same way given the guidance in the specification and the feature of carboxy terminal peptides recited in the claims. Thus, a person of skill could easily construct a library from any known G protein for use in the invention and not only those in Table III.

Applicants respectfully submit that every reason given by the Office as to why the claims are not enabled is either untrue or irrelevant to the claims here rejected. Applicants request reconsideration of the claims in light of the discussion above

and the claim amendments. Applicants have amended the claims to refer to carboxy terminal Gα peptides to advance prosecution in a previous amendment. Applicants submit that libraries composed of variant peptides based on the structure of G proteins are enabled because methods of making these libraries are provided, because the exact structure of each library member need not be individually specifically known to create, express or screen the library, and because the structure of the library is known: it is a peptide library based on a Gα subunit sequence. The Office has provided no concrete and reasonable explanation as to why any other Gα subunit could not be used the same way its family members are used.

"For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art [] would expect the claimed genus could be used in that manner without undue experimentation." M.P.E.P. §2164.03. Here, the specification provides several working examples using different GPCR/G protein-based library combinations, voluminous guidance concerning other GPCR and G proteins, numerous specific exemplary sequences on which libraries may be based, and guidance concerning the class generally. See ¶114-115. The Office has given no reason why one of skill would doubt that the screens of billions of compounds against seven different GPCR/G protein-based library pairs as provided in working examples here would not work for any GPCR with any library based on a GPCR-binding G-protein sequence that binds that GPCR. Therefore a rejection of this genus has no basis and should be withdrawn. For the foregoing reasons, Applicants request the Office withdraw the rejection of the claims based on lack of enablement and consider the new claim added here.

Claims 1, 3, 5-9, 13-19, 21-24 and 33 are rejected as obvious over Fowlkes et al. in view of Gilchrist "for reasons set forth in the Office Action." Since no reasons are explicitly provided in this Office Action, other than responses to Applicants' arguments, Applicants assume this refers to a previous Office Action. No previous Office Action, however, contains a rejection of any claims based on the combination of Fowlkes et al. and Gilchrist et al. on the grounds of obviousness. Since no reasons have been given for the rejection, Applicant submits that the Office has failed to meet its burden of showing a prima facia case of obviousness and the rejection should be withdrawn. Further, since no reasons were provided here, any further rejection on grounds of obviousness over these references should be a non-final Office Action.

The Office must meet three requirements to make out a prima facie case of obviousness. M.P.E.P. § 2143. The first requirement is that each and every element of the rejected claim must be taught or fairly suggested in the cited art, individually or in combination. It is therefore necessary to discuss the contents of each reference individually and in combination with the other cited references.

The primary reference, Fowlkes et al., is cited by the Office, in the Office Action dated June 11, 2003 as disclosing the method of Coughlin, which in turn is described by the Office as a method of identifying compounds by screening a library for agonizing or antagonizing receptor bioactivity. Fowlkes et al., as the Office concedes, teaches a traditional ligand assay in which (1) the ligand receptor is activated by an agonist and then (2) other compounds are added to test for their effect on the agonist's activation. This disclosure does not teach or fairly suggest anything about the GPCR/G protein interaction site or any

methods for testing for binding at this site. It is not even mentioned.

Leaving aside for the moment the difference in the receptors or receptor sites being assayed, however, the Fowlkes et al. reference also does not relate in any way to the type of two-step assay for identifying a GPCR signaling inhibitor which is claimed. Fowlkes et al. screen a first library for binding to the target protein to serve as surrogate ligands and then screen a second library for compounds that inhibit binding of a binding compound. Here, the native binding sequence is known. The first screening step is performed in the presence of this native binding sequence to discover library members that bind at a higher affinity than the native sequence. The claims have been amended here to clarify this step. Thus, not only does Fowlkes et al. lack any teaching or suggestion of the GPCR/G protein binding site, the library of peptides based on a Gα carboxyl terminal sequence, screening this library to select a binding peptide, or screening a second library in competition at the GPCR/G protein binding site with this selected peptide, it does not describe even a similar assay for the ligand receptor.

The Office characterizes the individual teaching of Fowlkes et al. in previous communications as encompassing three steps: (a) screening a first combinational library for binding to the target-binding ligands; (b) screening a second library for the ability to inhibit binding of a target-binding ligand; and (c) determining which of these inhibitory ligands can mediate an activity of the target protein.

With respect to step (a), the methods claimed here require screening in the presence of the native binding sequence, a feature not disclosed or even hinted at by Fowlkes et al. This step allows one to discover peptides that bind with a higher affinity than the native sequence. The Fowlkes et al. screen

identifies surrogates for an unknown ligand (p. 17, lines 18-23). With respect to step (b), the second screening step of the claims is done in competition with a high affinity binding peptide, not a surrogate ligand (of low affinity) and not to inhibit a target-binding ligand, but to identify a binder with even higher affinity than the previously selected peptide. The two steps of screening proposed by Fowlkes et al. (1) discover a ligand-surrogate peptide and then (2) find peptides that antagonize the binding of these surrogate ligands. Discovering high affinity binders is not even a goal in Fowlkes et al. The two steps of screening claimed here (1) discover a high affinity peptide that binds to the GPCR allosteric site with higher affinity than the (known) native binder and (2) find even higher affinity binding compounds. Each step of the two-step screen is different, and the total effect of the two steps is different. For example, in Fowlkes et al., the authors acknowledge in a prophetic example that the interactions they hope to study with their methods will likely be of considerably lower affinity than the native interactions (see page 79, lines 9-12). See also page 11, lines 35-38, which concede that the identified compounds of the "complementary" library will be less specific than the first library. The methods claimed here identify higher affinity compounds. The inventive methods are designed to reduce "false positives" by identifying only high affinity peptides and compounds, while Fowlkes et al. acknowledge this is a problem and propose testing the ligand surrogates for the ability to mediate the activity of the target protein to eliminate the false positives. The inventive methods avoid the need for this type of testing of the identified compounds and therefore provide an advantage. In addition, the compounds identified by the claimed screen would not mediate an activity of the target protein in any case, since they are not ligands. Furthermore, Fowlkes et al.

propose to use only target protein binding peptides that mediate the biological activity (i.e., function as ligands) for the second screening step. This is necessary in Fowlkes et al. to assure that the "surrogate ligands" actually do bind a relevant cite on the protein. It would not be necessary in the inventive methods because the inventive methods screen for binding to a known cite with a known binder to identify high affinity binders. These features distinguish the claimed screen from Fowlkes et al.

The Office cites Gilchrist for teaching the "motivation of non-traditional G-protein binding GPCR." The Office Action, page 18. However, Gilchrist does not teach the two step screen claimed here or any two-step screen. Fowlkes et al. describes screening proteins generally, for binding to any site on the protein, trusting that a site having potential interest will be bound by some of the screened peptides. The individual peptides would have to be tested for activity. The inventive methods do not require this type of confirmation because the screen is specific for a site already known to be of interest that has an already known native binding sequence. This is a fundamental difference between the invention and Fowlkes et al., and a reason why the general "fishing expedition" type of methods proposed by Fowlkes to discover binding sites and antagonists for them would not be used to study a known protein with a known receptor and a known native binder, such as the GPCR of Gilchrist. Applicants therefore submit that there is no motivation to combine the references.

However, even if the two references were combined by one of skill to use the methods of Fowlkes et al. with the G-protein binding GPCR of Gilchrist, the most one could achieve would be a GPCR assay where (1) a library of peptides was screened for binding to GPCR generally in the absence of the native sequence and (2)a second library was screened against those peptides that

bound. No high affinity compounds would be isolated and a large number of false positives would be identified, both in terms of affinity too low to be useful and in terms of the location of the binding since the Fowlkes et al. methods do not provide any mechanism for assuring that only peptides that bind strongly to the site of interest are identified. The Fowlkes et al. methods are forced to rely on traditional "lead optimization" techniques to sort out weak from strong binders. See Fowlkes et al., page 19, lines 6-9. This problem is one which the inventive screens are designed to circumvent by not identifying weak-binding compounds. Thus, even if the Fowlkes et al. methods were used with the Gilchrist receptor, the results would not be the same, therefore there could be no reasonable expectation of identifying only high affinity binding compounds.

Applicant submits that the Office cannot make out a prima facie case of obviousness based on the two cited references because it cannot meet even one of the three necessary criteria: (1) the combined art does not meet each and every limitation of the claims, (2) there is no motivation to screen the GPCR allosteric receptor using the Fowlkes et al. methods which do not describe screening <u>any</u> specific and known receptor interaction site and; (3) even if the disclosures were combined there would be no expectation of success.

Applicant request reconsideration of the rejections made herein and favorable consideration of the amended claims.

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